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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,470	07/21/2003	Debbi Drane	017227-0190	4517

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,470	DRANE ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 44-99* is/are pending in the application.

4a) Of the above claim(s) *56-63,77-83 and 86-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55, 63, 64-76, 84-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/21/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is to acknowledge the amendment filed on July 27, 2005. Claim 1 was amendment Claims 2-43 were canceled. New claims 44-99 were added. Claims 1 and 44-99 are pending.

Sequence requirements

This application contains sequence disclosures (See specification Table III and IV) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 64-85, group A of HCV core antigen with species of (d) of cardiolipin and (i) diphosphory lipid A in the reply filed on 12/20/2005 is acknowledged. The traversal is on the ground(s) that claim 64 should be a linking claim that links group A to H. If it is found to be allowable, the restriction requirement of group A to H should be withdrawn.

2. Applicants' argument has been fully considered; the claim 64 is now considered as linking claim that link group A to H together.

3. Claims 1 and 64 are link(s) inventions of groups A-J and H. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1 and 64. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional

application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

4. Regarding to the argument of group I and II for enjoinment, applicants' argument is persuasive, group I regarding to the elected core antigen in group A is also rejoined with the elected group II. Therefore, claims 1, 44-55, 63, 64-76, 84, 85 that read on group A of HCV Core antigen are considered before the examiner. Claims 56-62, 77-83 and 86-99 are withdrawn from the consideration.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 64-76, 84-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising HCV full length core antigen (1-191) adsorbed onto the case-like structure of ISCOMATRIX by ionic interaction,, wherein said Core-ISCOM immune complex is able to produce a strong cytotoxic T lymphocyte (CTL) immune response against a specific core antigen epitope or the said composition comprising the extra E1/E2 antigen in the presence of MF59 adjuvant that is able to produced an enhanced cytotocxic T lymphocyte response specifically against HCV epitopes in Rhesuaes macaques, does not reasonably provide enablement for having a vaccine composition comprising said antigen complex that is able to protect HCV infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

8. 1) & 2) State of art & Unpredictability of the filed. HCV encodes polyprotein Core, E1, E2, NS3 to NS5. However, being a RNA virus, HCV virus is subject to mutate rapidly and automatically in adapting the survival to the various environment challenges. HCV virus family therefore renders many heterogenic phenotypes and quasispecies among one single isolated clone. Thus, the state of art suggests that the most ideas of viral-clearance mechanisms remain hypothetical and none of the immunogenic compositions comprising HCV encoded proteins have been approved to be successfully used for controlling or preventing the HCV infection (See detail discussions by Dr. Robert Purcell, Hepatology 1997, Vol. 26, pp. 11S-14S), and Farci et al. Science, 2000, Vol. 289, pp. 2003a.). In conclusion, the field of developing HCV vaccine is extremely unpredictable. The art therefore, suggests that any vaccine should be tested in an big primate animal model for the approval of its efficacy.

9. 3) &4). Number of working examples and Amount of guidance. The specification of the present applicant only presents that full length of HCV core protein (aa 1-191) is formulated with the negative charged adjuvant ISCOM or the said the composition further comprises an extra E1 and/or E2 antigen formulated with adjuvant MF59 (E1E2 + Core- ISCOM™) are used for priming the animal, which produce a strong specific $CD8^+$ and $CD4^+$ T cell response against certain peitope of HCV virus. However, there is no working examples or guidance that injection of said immunogenic composition is able to produces a sustained immunity that is able to prevent HCV infection. Applicants are reminded that a limited in vitro experimental result cannot be extrapolated into a result from an in vivo setting experiment.

10. 5) Scope of the claims. The claims broadly on read on an immunogenic complex or a vaccine composition comprising any or all charged HCV antigens with any or all charged organic carrier that are able for preventing or treating HCV infection.

11. 6). Nature of the invention and technical requirement within level of skill in the art. Therefore, the level of the skill in art is very high because the significant quansisspecies of HCV and significant and frequent mutation of the HCV genome.

12. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 46-55, 63, 64, 66-76, 85 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/15287A1.

15. WO 98/15287A1. discloses an immunogenic composition comprising an antigen or antigen and adjuvant. The said antigen is HCV antigen and the adjuvant that is a negative charged adjuvant, QS21 and sopanin associated with liposome or an ISCOM comprising a phospholipid, De-O-acetated monophosphoryl lipid A and a sterol. The sopanin or ISCOM is naturally occurring negative charged carrier for any positive charged HCV antigen. The addition of the De-O-acetated monophosphoryl lipid A, which is inherently by its chemical characteristic enhance the association between the positive charged antigen and negative charged adjuvant. This novel adjuvant formulation elicit an enhanced both Th2 and Th1-type immune responses, which is characterized by high INF-λ, T-cell proliferation and CTL response (see Figs. 1-7 and claims 1-7). Therefore, the claimed invention is anticipated by the cited reference.

16. Claims 1, 46-55, 63, 64, 66-76, 85 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 99/11241A1,

17. WO 99/11241A1, disclose an immunogenic composition comprising HCV antigen or antigen preparation in an oil-in-water emulsion, which comprises a negative charged adjuvant, sopanin, QuilA or its derivative. The composition further comprises cholesterol and De-O-acetated monophosphoryl lipid A, which inherently become the ISCOM complex. Either Sopanin or ISCOM is naturally occurring negative charged adjuvant and the addition of De-O-acetated monophosphoryl lipid A enhances the electrostatically association between the adjuvant with an antigen by its chemical characteristic. This novel adjuvant formulation elicit an enhanced both Th2 and Th1-type immune responses, which is characterized by high INF-λ, T-cell proliferation and CTL response (see lines 7 on page 54 through line 5 on page5, and claims 1-28). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1, 44-55, 63, 64-76, 84-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/15287A1 and Coppoer et al. (Immunity, 1999, April, Vol. 10, pp. 439-449) and John et al. (Hepatology 1999, Vol. 30, No. 4, pp. 1037-1044)

20. The claimed invention is drawn to an immunogenic composition comprising HCV full length core antigen (1-191) adsorbed onto the case-like structure of ISCOMATRIX by ionic interaction,, wherein said Core-ISCOM immune complex is able to produce a strong cytotoxic T lymphocyte (CTL) immune response against a specific core antigen epitope or the said composition comprising the extra E1/E2 antigen in the presence of MF59 adjuvant that is able to produced an enhanced cytotocxic T lymphocyte response specifically against HCV epitopes in

Rhesuaes macaques, does not reasonably provide enablement for having a vaccine composition comprising said antigen complex that is able to protect HCV infection.

21. WO 98/15287A1. discloses an immunogenic composition comprising an antigen or antigen and adjuvant. The said antigen is HCV antigen and the adjuvant that is a negative charged adjuvant, QS21 and sopanin associated with liposome or an ISCOM comprising a phospholipid, De-O-acetated monophosphoryl lipid A and a sterol. The sopanin or ISCOM is naturally occurring negative charged carrier for any positive charged HCV antigen. The addition of the De-O-acetated monophosphoryl lipid A, which is inherently by its chemical characteristic enhance the association between the positive charged antigen and negative charged adjuvant. This novel adjuvant formulation elicit an enhanced both Th2 and Th1-type immune responses, which is characterized by high INF-λ, T-cell proliferation and CTL response (see Figs. 1-7 and claims 1-7). WO 98/15287A1 does not explicitly teach which HCV antigen should be used.

22. Cooper et al. disclose several HCV immunogenic epitopes with about 10 amino acids long; and method for idenitying such immunogenic epitopes that are able to induce a strong cytotoxic T lymphocyte (CTL) immune response against HCV antigen. The CTL specific targeting epitopes are found to be restricted by all MHC class I allotypes and they locate at six viral regions (C, E1, E2, NS1, NS3, NS4 and NS5). However, the animals with chronic hepatitis only generate a weaker acute CTL responses.

23. John et al. teach several HCV T cell epitope in Core antigen and envelope antigen that all have about 10 amino acids in size, and are able to induce a significantly T cell mediated immune response for variants of different HCV stains (See entire document, especially, Table 2 and Fig. 4). Moreover, John et al. teach that while HCV genetic mutation rate is high, the coding mutation was decrease in HCV core antigne region and increase in envelope region. No genetic mutation was seen in any of the core CTL epitope despite detectable cellular response (See abstract).

24. Therefore, it would have been obvious for an artisan with ordinary skill in the art to be motivated by the disclosures of WO 98/15287A1, Cooper et al. and John et al. to make an immunogenic composition mainly by using the antigen epitopes from the core antigen taught by Cooper and John plus an adjuvant disclosed by WO 98/15287A1, because John et al teach that the HCV Core antigen is more reliable for inducing a T cell mediated immune response among different isolates against HCV infection since it has less mutation among different isolates of

HCV, and the addition of adjuvant disclosed by WO 98/15287A1 will remedy the week immune response of Core antigen disclosed by John and Cooper. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BAOQUN LI, MD
PATENT EXAMINER

Bao Qun Li
1/06/2006